REMARKS

Reconsideration of this application is requested in view of the amendments to the claims and the remarks presented herein.

The claims in the application are claims 23, 25, 26, 28 to 31, 35 to 39, 41 and 43, all other claims having been cancelled. Generic claim 23 has been redrafted in order to improve clarity and to limit its scope to the main industrial application of the invention that is sought by the Applicant, namely, the use of a lipopeptide as defined in the specification wherein the said lipopeptide contains a single lipid moiety consisting of an unbranched or branched, unsaturated or saturate chain derived from fatty acids of 10 to 20 carbon atoms. The lipopeptides are those of the CTL epitope consisting of a CTL epitope of an HIV protein as specified in pending claim 40. Claim 23 has been modified to detail separately the various embodiments of the location of the amino acid spacer chains either (i) between the lipid moiety and the epitope, (ii) between two distinct epitopes or (iii) at both locations. It is believed that the redrafted claims obviate the rejection based under 35 USC 112, first paragraph, since it is believed that the claims are based upon an enabling disclosure and obviates the rejection based on 35 USC 112, second paragraph. Therefore, withdrawal of these grounds of rejection is requested.

Claims 23, 24, 30, 34 to 37, 40 and 43 stand rejected under 35 USC 102 as being anticipated by the Kubo et al patent. The Examiner states that the Kubo et al patent

discloses two molecules of palmitic acids linked through a Lys containing amino acid linker to a multi-valent T helper/auxiliary epitope QYIKANSKFIGITE from tetnus toxin and further linked to a melanoma CTL peptide epitope either directly or using a spacer as indicated in columns 7 and 8 and also it discloses vaccines comprising the lipopeptides in lines 15 to 25 of column 2.

Applicants respectfully traverse this ground of rejection since the Kubo et al patent neither anticipates nor renders obvious Applicants' invention. The reference is directed to immunogenic constructs that could be, in some embodiments, presented under the form of lipopeptides but there is no specific lipopeptide disclosed in the reference. When it refers to prior art lipopeptides, this is directed only to tripalmitoyl lipopeptides as indicated in lines 59 to 63 of column 8. Therefore, Kubo et al does not disclose any lipopeptide containing a single lipid moiety. Moreover, the reference does not disclose any lipopeptide containing a CTL epitope consisting of a CTL epitope of an HIV protein. Therefore, the reference neither anticipates nor renders obvious Applicant's invention.

The superiority of a lipopeptide having a single lipid moiety is clearly understood from the specification and specifically, the examples. The most efficient lipopeptides are those that comprise only one single lipid moiety as illustrated in the examples by the lipopeptide comprising a single palmitoyl chain also indicated as "Monopalm". The synthesis of the mono-palmitoyl lipopeptide is disclosed in Example 2. Fig. 4 shows that

the mono-palmitoyl lipopeptide is most efficient when compared to dipalmitoyl lipopeptide as can be seen from their respective properties of inducing $CD8^+$ as indicated in section 4 of Example 3. Moreover, the mono-palmitoyl derivatives are water soluble whereas the di-palmitoyl derivatives are soluble only in a water-DMSO mixture as can be seen from Example 5.

It can also be clearly seen in Fig. 6B that the mono-palmitoyl lipopeptides are far more efficient than the dipalmitoyl lipopeptides in inducing a CTL response as can be seen from Example 5. Moreover, Figure 7A shows the better properties of the mono-palmitoyl lipopeptides as compared to the dipalmitoyl lipopeptides to induce a $CD8^+$ response as can be seen from lines 10 to 15 of page 24 of Example 5. Also, Figs. 8A and 8B show the high potency of a mono-palmitoyl lipopeptide to induce the production of a $CD8^+$ response as indicated in section 3 of Example 5. Therefore, it is deemed that the lipopeptide containing a single lipid moiety is patentably distinct.

Claims 23 to 25, 30, 34 to 37, 40 and 43 were rejected under 35 USC 103 as being obvious over the Vitello et al reference taken in view of the '824 patent and patent publication No. 719A1. The Examiner states that the Vitello et al reference teaches that most CTL peptide epitopes are poor immunogens so modification by attaching a T helper peptide (HTL) epitope such as tetnus toxiod peptide 830-843 and two lipid molecules such as palmitic acid improves immunogenicity and results in long term-memory CTL induction. The Examiner concedes that the primary reference does not teach that the

linker separating the T helper epitope and the CTL epitope comprises charged amino acid residues. The '824 patent is cited to show fusion proteins comprising a domain having a hydrophilic spacer comprising either Lys or Arg in lines 57 and 58 of column 6 and the sentence spanning columns 6 and 7 and that the patent discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be oriented with an exposed regions of the fusion protein and increases the likelihood that the linker will be accessible to digestion. The '719 published application is cited to show peptides such as class I MHC antigens and class II MJHC are particularly intractable to transmembrane transport and that polymers of highly basic subunits such as Arg attached to the peptide can facilitate transport across the cell membrane. The Examiner deems it would have been obvious to one skilled in the art to have added a hydrophilic spacer comprising either Lys or Arg disclosed by the '824 patent and the '719 published application between the HTL and CTL epitope and in between the HTL and lipopeptide taught by Vitello et al.

Applicants respectfully traverse this ground of rejection since none of the references cited by the Examiner relate to a lipopeptide containing a single lipid moiety. The Vitello et al reference discloses only dipalmitoyl lipopeptides as can be seen from the Abstract and Table 1 on page 344. The secondary references also lack any disclosure of any lipopeptide. The '824 patent discloses a system for expressing fusion proteins wherein the fusion proteins can contain a hydrophilic spacer chain. The published '719 application discloses peptides that are coupled to amino acid chains for transport across

biological membranes. However, none of the secondary references overcome the lack of teaching of Vitello et al with respect to the use of effective lipopeptides containing a single lipid moiety. Therefore, this ground of rejection fails and withdrawal of the same is requested.

Claims 23, 24, 30, 35, 36, 40 and 43 were rejected under 35 USC 103 as being obvious the Wiesmuller et al reference taken in view of the Lasarte et al reference. The Examiner states that the Wiesmuller et al reference teaches lipopeptides with adjuvant activity comprising a hydrophilic linker such Pam3Cys-Ser$(Lys)_4$ and further comprising an antigenic peptide EGFR 516-529 or antigenic HIV gp peptides or antigenic Influenza NP peptides. Wiesmuller et al allegedly teaches that the lipopeptides are adjuvants and the secondary reference is cited to show peptide construct such as HTL-KK-K-CTL i.e. a T helper epitope linked to two Lys residues linked to a CTL epitope including to an HIV gp 120 peptide epitope. The Examiner deems that it would have been obvious to one skilled in the art to more easily internalize the peptide construct of Lasarte et al since Wiesmuller et al teaches the importance of the superior properties of using the lipid moiety of lipopeptides as adjuvants and to facilitate uptake by APC. Lasarte et al teaches the need for both internalization and TC help in the efficient in vivo priming of CTL.

Applicants respectfully traverse this ground of rejection since the combination of the prior art cited by the Examiner does not render obvious Applicants' invention. The Wiesmuller et al reference only discloses tripalmitoyl lipopeptides and would not suggest

to one skilled in the art the use of a lipopeptide containing a single lipid moiety as can be seen from Table 1 on page 256. The Lasarte et al reference discloses only peptide conjutgates and not lipopeptides. Therefore, one skilled in the art would not combine the Lasarte et al teachings with Wiesmuller et al with regard to the use of a peptide containing a single lipid moiety and therefore, withdrawal of this ground of rejection is requested.

Claim 37 was rejected under 35 USC 103 as being obvious over the Wiesmuller et al reference taken in view of the Lasarte et al reference taken in further view of the Oseroff et al reference.

Applicants respectfully traverse this ground of rejection since the combination of the primary, secondary and tertiary art would not suggest Applicants' invention to one skilled in the art. The deficiencies of the Lasarte et al and Wiesmuller et al combination is discussed above and the Oseroff et al reference merely discloses dipalmitoyl lipopeptides and not lipopeptides containing a single lipid moiety as can be seen from Table 1 on page 824. Therefore, withdrawal of this ground of rejection is requested.

Claim 25 was rejected under 35 USC 103 as being obvious taken in view of the Wiesmuller et al reference, in view of the Lasarte et al reference and in further view of

the '824 and Alberts et al reference. The '824 patent allegedly discloses fusion proteins comprising a domain having a hydrophilic spacer comprising either Lys or Arg and Alberts et al is cited to show that the $C=NH2^{+}$ group of arginine is very basic because its positive charge is stabilized by resonance. The Examiner deems it would be obvious to modify Wiesmuller et al and Lasarte et al by using a spacer comprising arginine in place of lysine.

Applicants respectfully traverse this ground of rejection since the combination of the primary, secondary and tertiary art, which the Examiner has made with the benefit of Applicants' disclosure, would not suggest Applicants' invention to one skilled in the art. The deficiencies of the Wiesmuller et al and the Lasarte et al combination is described above and the Alberts et al and the '824 patent do not overcome the fallacy of this combination of the prior art. The Alberts et al reference only shows that the arginine amino acid residue is positively charged. It cannot overcome the lack of the teaching of Wiesmuller et al and the other documents as teaching a single lipid moiety as Applicants claim. Therefore, withdrawal of this ground of rejection is requested.

Claims 23, 24, 30, 35, 37, 40 and 43 were rejected under 35 USC 103 as being obvious over the Bessler et al reference taken in view of the IDS reference and and the '395 patent. The Examiner states that Bessler et al teaches lipopeptides comprising as lipids such as three molecules of polymidic acid, a linker such as $S)K)_4$ i.e. positively

charged amino acid residue linked to a T helper epitope. The Examiner concedes that Bessler et al does not teach the HTL and CTL epitopes being separated by linker comprising charged amino acid residues. The IDS reference is cited to show a HIV peptide epitope comprising the sequence GPGR linked by an anionic spacer of 1 and 5 amino acid residues plus or minus a neutral spacer. The '395 patent is cited to show the use of auxiliary HTL epitopes linked to CTL epitopes by a spacer amino acid linker and further linked with palmitic acid or lipid moieties. The Examiner deems it would have been obvious to use the anionic spacer of the IDS reference to separate the HTL and CTL epitopes in the lipopeptide of Bessler et al for the lipopeptides disclosed by the '395 patent.

Applicants respectfully traverse this ground of rejection since the combination of the prior art that the Examiner has cited with the benefit of Applicants' invention would in no way teach Applicants' invention to one skilled in the art. Bessler et al is exclusively directed to tripalmitoyl lipopeptides and therefore, it does not overcome the lack of the teachings of the prior art documents wherein Applicants' invention is directed to the single lipid moiety. The secondary art cited by the Examiner does not overcome the deficiencies of the Bessler et al patent. The IDS reference discloses immunogenic constructs comprising a CTL and HTL epitope linked together through a spacer but does not disclose any lipopeptide. The '935 patent relates exclusively to dipalmitoyl and tripalmitoyl lipopeptides as can be seen from line 60 of column 5 through line 45 of

column 6 and line 27 of column 8. Therefore, the combination of the prior art cited by the Examiner would not suggest a lipopeptide containing a single lipid moiety. Therefore, withdrawal of this ground of rejection is requested.

In summary, the prior art documents cited by the Examiner are always concerned with dipalmitoyl or tripalmitoyl lipopeptides as the solution for inducing an immune response but none of these documents would lead one skilled in the art to manufacture lipopeptides having a single lipid moiety for an effective induction of a CTL response against an antigen of interest and A Fortiore against an HIV protein. The other document cited by the Examiner are not relevant since they do not relate at all to lipopeptides and do not overcome the deficiencies of the teachings of the primary references. Therefore, they would in no way anticipate or render obvious Applicants' invention.

In view of the amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
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Enclosure